Abstract

This application pertains to methods and compositions that modulate proliferation and/or differentiation of undifferentiated mesodermally-derived cells so as to have an effect on at least one of vascular growth and hematopoiesis.

In the claims:

For the convenience of the Examiner, all claims being examined, whether or not amended, are presented below.

Please cancel claims 76-81 (as originally numbered) without prejudice.

57. (Amended) A method of stimulating a population of undifferentiated mammalian mesodermally derived cells to undergo hematopoiesis, comprising contacting the cells with a hedgehog compound so as to stimulate the cells to undergo hematopoiesis.

58. (Amended) A method according to claim 57, wherein the hedgehog compound is selected from Indian hedgehog, Desert hedgehog, and Sonic hedgehog proteins and fragments thereof which bind to *patched.*

59. (Amended) A method according to claim 57, wherein the hedgehog compound is an Indian hedgehog protein or fragment thereof which binds to *patched.*

60. (Amended) A method according to claim 80, wherein the TGF-β compound is a bone morphogenic protein.

61. (Amended) A method according to claim 60, wherein the bone morphogenic protein is selected from BMP-2, BMP-4, BMP-6, and BMP-7.

62. (Amended) A method according to claim 57, further comprising maintaining the cell population in vitro in a culture medium, and wherein contacting the cells with a hedgehog compound includes contacting the cells with a culture medium comprising the hedgehog compound.

63. (Amended) A method according to claim 57, wherein the undifferentiated mesodermally derived cells are hematopoietic stem cells.

64. (Amended) A method according to claim 63, wherein the hematopoietic stem cells are selected from cord blood cells, fetal liver cells, and peripheral blood cells.

65. (Amended) A method according to claim 63, wherein the hematopoietic stem cells are obtained from adult bone marrow cells.

66. (Amended) A method according to claim 57, wherein the cells are progenitor cells obtained from an adult human.

67. (Amended) A method according to claim 57, wherein the cells constitute embryonic tissue.

68. (Amended) A method according to claim 57, wherein the cells constitute an embryonic explant culture.

69. (Amended) A method according to claim 68, wherein the embryonic explant culture is a blastocyst.

70. A method according to claim 57, wherein the cells are hematopoietic stem cells within the bone marrow of an animal.

71. (Amended) A method according to claim 57, wherein the cells are hematopoietic stem cells present in the animal in at least one of bone marrow, cord blood cells, fetal liver cells and peripheral blood cells.

72. (Amended) A method according to claim 70, wherein contacting the stem cells with the hedgehog compound includes administering an effective dose of the compound to the animal by any of oral, intradermal, subcutaneous, transmucosal, intramuscular, or intravenous routes.

73. (Amended) A method according to claim 80, wherein the second compound, enhances the stimulation of hematopoiesis of the cells by more than the amount of stimulation of hematopoiesis resulting from administration of an identical amount of the second compound in the absence of the hedgehog compound.

Please add the following new claims:

80. (New) A method according to claim 57, further comprising contacting the cells with a second compound comprising a TGF-β compound.

81. (New) A method of stimulating hematopoiesis in an animal, comprising administering to the animal a hedgehog compound, whereby cells in the animal are stimulated to undergo hematopoiesis.

82. (New) A method according to claim 80, wherein the hedgehog compound is selected from Indian hedgehog, Desert hedgehog, and Sonic hedgehog proteins and fragments thereof which bind to *patched.*

83. (New) A method according to claim 80, wherein the hedgehog compound is an Indian hedgehog protein or fragment thereof which binds to *patched.*

84. (New) A method according to claim 80, further comprising contacting the cells with a second compound comprising a TGF-β compound.

85. (New) A method according to claim 84, wherein the TGF-β compound is a bone morphogenic protein.

86. (New) A method according to claim 85, wherein the bone morphogenic protein is selected from BMP-2, BMP-4, BMP-6, and BMP-7.

87. (New) A method according to claim 80, wherein the undifferentiated mesodermal-derived cells are a population of hematopoietic stem cells.

88. (New) A method according to claim 87, wherein the hematopoietic stem cells are selected from cord blood cells, fetal liver cells, and peripheral blood cells.

89. (New) A method according to claim 80, wherein the cells are human progenitor cells.

90. (New) A method according to claim 80, wherein the cells are hematopoietic stem cells within the bone marrow of the animal.

91. (New) A method according to claim 80, wherein the cells are hematopoietic stem cells present in the animal in at least one of bone marrow, cord blood cells, fetal liver cells and peripheral blood cells.

92. (New) A method according to claim 80, wherein an effective dose of the hedgehog compound is administered to the animal by any of oral, intradermal, subcutaneous, transmucosal, intramuscular, or intravenous routes.

The claims presented above incorporate changes as indicated by the marked-up versions below.

57. (Amended) A method of stimulating a population of undifferentiated mammalian mesodermally derived cells to undergo [at least one of] hematopoiesis[, endothelial cell differentiation and proliferation], comprising[:]

[(a) providing a first compound selected from the group consisting of hedgehog and WNT and optionally a second compound comprising a TGF-β; and

(b)] contacting the cells with [the one or more compounds] <u>a hedgehog compound</u> so as to stimulate the cells to undergo [at least one of] hematopoiesis[, endothelial differentiation and endothelial proliferation].

58. (Amended) A method according to claim 57, wherein the hedgehog compound is selected from [the group consisting of] Indian hedgehog, Desert hedgehog, and Sonic hedgehog proteins and fragments thereof which bind to *patched* [compound].

59. (Amended) A method according to claim 57, wherein the hedgehog compound is an Indian hedgehog protein or fragment thereof which binds to *patched* [compound].

60. (Amended) A method according to claim [57] 80, wherein the TGF-β compound is a bone morphogen[et]ic protein[s].

61. (Amended) A method according to claim [57] 60, wherein the bone morphogen[et]ic protein is selected from [the group consisting of] BMP-2, BMP-4, BMP-6, and BMP-7.

62. (Amended) A method according to claim 57, further comprising [the step of] maintaining the cell population in vitro in a culture medium, and wherein [such that step (b) includes] contacting the cells with a hedgehog compound includes contacting the cells with a culture medium comprising the hedgehog compound [in the culture medium].

63. (Amended) A method according to claim 57, wherein the undifferentiated mesodermally [-] derived cells are [a population of] hematopoietic stem cells.

64. (Amended) A method according to claim [57] 63, wherein the hematopoietic stem cells are selected from [the group consisting of] cord blood cells, fetal liver cells, and peripheral blood cells.

[67] 65. (Amended) A method according to claim [65] 63, wherein the hematopoietic stem cells are obtained from adult bone marrow cells.

[68] 66. (Amended) A method according to claim 57, wherein the cells are progenitor cells obtained from an adult human.

[69] 67. (Amended) A method according to claim 57, wherein the cells constitute embryonic tissue.

[70] 68. (Amended) A method according to claim 57, wherein the cells constitute an embryonic explant culture.

[71] 69. (Amended) A method according to claim [70] 68, wherein the embryonic explant culture is a blastocyst.

[72] 70. A method according to claim 57, wherein the cells are hematopoietic stem cells within the bone marrow of an animal.

[73] 71. (Amended) A method according to claim 57, wherein the cells are hematopoietic stem cells present in the animal [and are selected from the group of hematopoietic cells found] in at least one of bone marrow, cord blood cells, fetal liver cells and peripheral blood cells.

[74] 72. (Amended) A method according to claim [72] 70, [further comprising; causing the compound to] wherein contacting the stem cells with the hedgehog compound includes [by] administering an effective dose of the compound to the animal by any of oral, intradermal, subcutaneous, transmucosal, intramuscular, or intravenous routes.

[75] 73. (Amended) A method according to claim [57] 80, wherein [the first compound is capable of acting synergistically with] the second compound, [so as to] enhances the stimulation of [at least one of] hematopoiesis of the cells by more than the amount of stimulation of hematopoiesis resulting from administration of an identical amount of the second compound in the absence of the hedgehog compound [, endothelial cell proliferation and endothelial cell differentiation].